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TRANSITION METAL CHELATES OF GLUCOSAMINES AS CW-AGENT-SPECIFIC CATALYSTS

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Abstract

In connection with the development of a stable biopolymeric catalyst system based on metal-coordinated chitosan, studies were undertaken on the thermodynamic stabilities and catalytic activities of model compounds consisting of 1:1 and 1:2 Cu(II)-chelates of glucosamine oligomers. In the combined presence of selected bidentate nitrogen donors, the destabilization of the 1:1 chelates involving their hydrolysis and disproportionation was obviated through additional coordination of the central metal ion. Their stability and mode of coordination were determined by the potentiometric equilibrium pH method and circular dichroism (CD) and electron pharmagnetic resonance (EPR) spectral methods. The stability constants for the 1:1 and 1:2 Cu(II)-chelates of glucosamine (GA), methoxyglucosamine (MGA), chitobiose (CB), chitotriose (CT) and chitotetrose (CTet) were respectively, β_1, = 9.88, 9.61, 10.50, 6.84 and 8.24, and β_2 = 17.96, 17.53, 17.15, 10.83 and 11.91. The rates of decomposition of Sarin and Soman in aqueous 0.02 M PIPES buffer (pH 7.2) by the binary and ternary chelates were determined. The catalytic activities of the chelates were examined in the perspective of their stabilities, structures and percent species distribution. On this basis, two possible mechanisms are presented.

Background

In connection with the exploration of the Cu(II) chelates of chitosan (a natural biopolymer) as a potential catalyst system for the decomposition of chemical warfare (CW) agents, an investigation of the nature of metal coordination with the monomeric glucosamine and its di-, tri- and tetrameric oligomers was undertaken. It is conceivable that a study of the thermodynamic equilibria of these metal chelates and their reactivity toward CW-agents could constitute a useful basis for the Cu(II)-chitosan system. Although studies on the interaction of Cu(II) with glucosamine have been reported in the literature (1-3) its destabilizing tendency to hydrolyze and disproportionate has not been addressed. Importantly, we have examined in the present study the coattachment of an additional mole of a second ligand that would lead to the formation of a hydrolytically stable ternary chelate of Cu(II)-glucosamine oligomers. The information thus generated would help establish a useful chemical basis for devising a stable Cu(II)-chitosan system suitable for catalytic activity.

Martell et al., reported the metal chelate catalyzed hydrolysis of diisopropylphosphorofluoridate (DFP) and isopropylmethylphosphonofluoridate (Sarin) (4-5). The possible application of hydrolytically stable ternary chelates of Cu(II) has not been considered so far. Hence, the objective of our study is to investigate the formation of ternary chelates of Cu(II)-glucosamine oligomers with neutral bidentate amines and their CW-agent-decomposing characteristics.

Materials and Methods

Aqueous stock solutions (0.02 M) of D-glucosamine, methoxyglucosamine and the other bidentate nitrogen donor amines were prepared by dissolving appropriate quantities of the respective (reagent grade) amine hydrochlorides in CO_2-free distilled water, standardized by potentiometric titration and stored in the refrigerator. Aqueous stock solution (0.02M) of copper (II) was prepared by using reagent grade copper nitrate and standardized by complexometric titration (6) against EDTA.

The potentiometric equilibrium pH method was used in this investigation. The method consists in determining the proton association equilibria of the different amines (hydrochlorides) in the presence and in the absence of Cu(II) ion in equimolar or higher molar ratios means of a glass-calomel electrode system in a thermostatted electrometric cell. All the titrations were carried out at 25.0 ± 0.1°C and strength of 1.0 (1.0 M KNO_3). Using the potentiometric data, titration curves for the different metal-ligand systems were traced (Figure 1). Possible metal-binding reactions occurring in solutions were then postulated on the basis of an analysis of the potentiometric equilibrium curves. The reaction thus assumed constituted the basis for appropriate mathematical treatments and the determination of the metal chelate formation constants. [The magnitude of the binding constant is a measure of the strength of metal-ligand binding]. Details of the potentiometric equilibrium pH method were reported in a number of earlier publications (7-11).

The calculations of the metal chelate stability constants and the distribution of the different chelate species over the pH range 2-12 were carried out with a computer program (BEST) provided by Dr. R. J. Motekitis and Dr. A. E. Martell, Texas A&M University, College Station Texas.

EPR spectra of the metal chelates were taken by using a Bruker Model ER 200D-SPC Electron Spin Resonance Spectrometer with an ESP data system, an ER 04/MR microwave bridge and a BVT-1000 Variable Temperature controller. EPR measurements were made at two temperatures, viz., 77°K and 150°K. Circular dichroism (CD) spectra of the metal chelates were recorded in the wavelength range 800-240 nm on AVIV 61 DS Solid State instrument. The instrument was equipped with a 50 kHz photoelastic modulator and an end-on photomultiplier and was interfaced with an AT&T computer.

The rates of hydrolysis of DFP, DIMEBU (3,3-dimethylbutylmethylphosphonofluoridate), SOMAN and SARIN brought about by the Cu(II) chelates was determined by using a fluoride ion electrode to measure the amount of F^- produced by the hydrolysis of the substrate. The reactions were conducted at 25°C in 2 x 10^{-2} M pH 7.2 pipes (piperazine-N,N^1-bis[2-ethane-sulfonic acid]) with 0.4 M KCl. The fluoride ion electrode was calibrated with 2 x 10^{-3} M and 2 x 10^{-5} M NaF standards in the pipes buffer, and the electrode efficiency was better than ~97% throughout the test period.

Stock solutions of copper nitrate and the ligands for the agent-hydrolysis experiments were prepared as described earlier and standardized. Both the neat Soman and DFP were less than 1% hydrolyzed but the neat Sarin was about 10-12% hydrolyzed.

The agent-hydrolysis experiment was begun by adding 22 or 23 ml of the pipes buffer to the temperature-controlled (jacketted) cell and placing the F^- electrode in the buffer. Next 0.1 millimole of the neat agent was added to the buffer and the rate of hydrolysis without catalyst was measured for 10 minutes. Then 0.1 millimole of the Cu(II) chelate was added and the final solution volume was made up to 25 ml. The concentration of the chelate and the initial concentration of the agent was each 4 x 10^{-3} M in all of the tests. The hydrolysis of the agent in the presence of the Cu(II) chelate was then recorded for 10 to 20 minutes. In tests with a slow (less than 4 μmoles/min) hydrolysis rate, the rate was constant throughout the test period and the constant value was recorded. The tests with high rates of hydrolysis showed a substantial decrease in the hydrolysis rate as the agent concentration decreased during the test period. Thus, when the hydrolysis rate was greater than 4 μmoles/min, the largest change in [F^-] per minute was recorded.

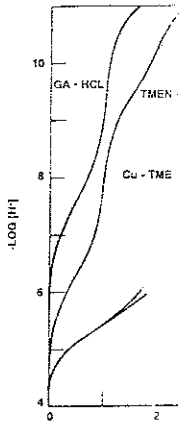

FIGURE 1. INTERACTIO... DIAMINE WITH

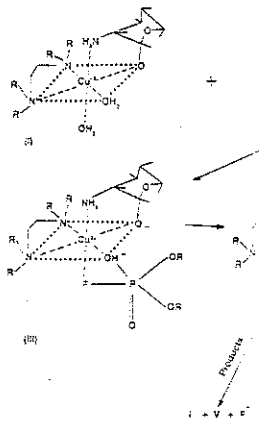

FIGURE 5. MECHANISM-1 FOR THE CATALYSIS BY

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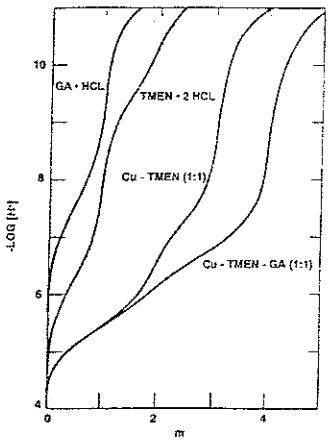

FIGURE 1. INTERACTIONS OF TETRAMETHYLETHYLENE DIAMINE WITH Cu(II) AND Cu(II)-GLUCOSAMINE.

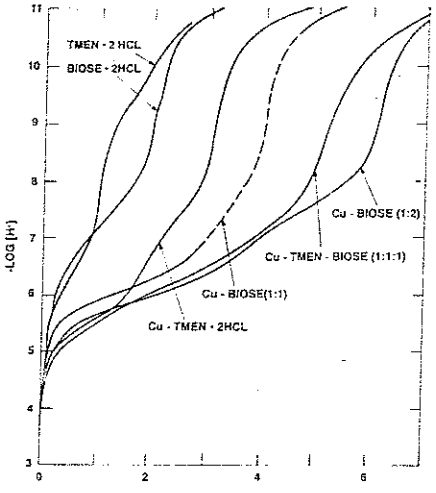

FIGURE 2. INTERACTIONS OF CHITOBIOSE WITH Cu(II) AND Cu(II) - TMEN.

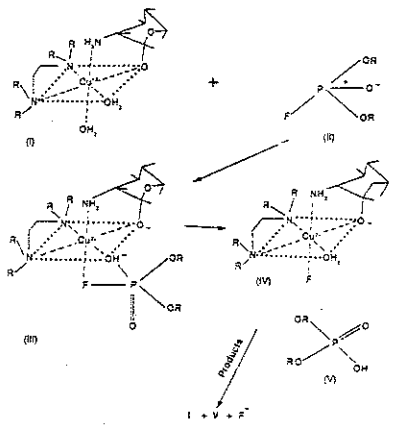

FIGURE 5. MECHANISM-1 FOR THE CATALYSIS BY TERNARY Cu(II)-CHELATE

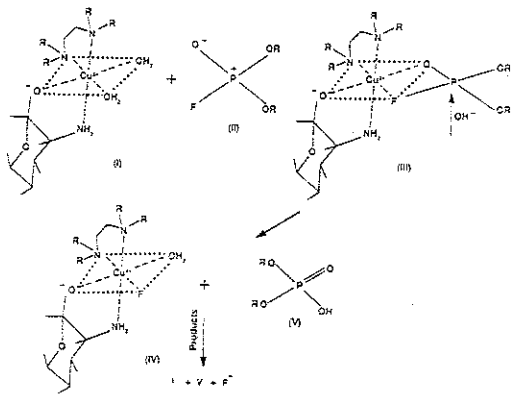

FIGURE 6 MECHANISM-2 FOR THE CATALYSIS BY TERNARY Cu(II)-CHELATE.

Table 1. Equilibrium Interactions of Cu(II) with Glucosamine and Glucosamine Oligomers

Ligand	Reaction Equilibria	Log of Chelate Stability Constant
Glucosamine (A)	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	9.88 ± 0.02
	$CuA^+ + A^- \rightleftharpoons CuA_2$	8.08 ± 0.02
Glucosamine (A) + Ethylenediamine (L)	$Cu^{2+} + L \rightleftharpoons CuL^+$	10.68 ± 0.04
	$Cu^{2+} + L + A^- \rightleftharpoons CuLA^+$	19.37 ± 0.02
Glucosamine (A) + Tetramethylethylenediamine (L)	$Cu^{2+} + L \rightleftharpoons CuL^{2+}$	7.57 ± 0.02
	$Cu^{2+} + L + A^- \rightleftharpoons CuLA^+$	16.34 ± 0.02
Glucosamine (A) + Tetraethylethylenediamine (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	10.24 ± 0.03
Glucosamine (A) + Diethylethylenediamine (L)	$Cu^{2+} + L \rightleftharpoons CuL^{2+}$	9.05 ± 0.01
	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	17.80 ± 0.01
Glucosamine (A) + Dipyridyl (L)	$Cu^{2+} + L \rightleftharpoons CuL^{2+}$	7.11 ± 0.01
	$Cu^{2+} + L + A^- \rightleftharpoons CuLA^+$	15.94 ± 0.09
Methoxyglucosamine (A)	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	9.61 ± 0.03
	$CuA^+ + A^- \rightleftharpoons CuA_2$	7.92 ± 0.03
Methoxyglucosamine (A) + Dipyridyl (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	15.85 ± 0.03
Methoxyglucosamine (A) + Tetramethylethylenediamine (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	15.39 ± 0.08
Methoxyglucosamine (A) + Ethylenediamine (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	18.77 ± 0.03
Chitobiose (A)	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	10.50 ± 0.03
	$CuA^+ + A^- \rightleftharpoons CuA_2$	6.65 ± 0.04
Chitobiose (A) + TMEN (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	15.82 ± 0.03
Chitotriose (A)	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	6.84 ± 0.05
	$CuA^{2+} + A^- \rightleftharpoons CuA_2$	3.99 ± 0.05
Chitotriose (A) + TMEN (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	12.51 ± 0.05
Chitotetrose (A)	$Cu^{2+} + A^- \rightleftharpoons CuA^+$	8.24 ± 0.04
	$CuA^{2+} + A^- \rightleftharpoons CuA_2$	3.67 ± 0.07
Chitotetrose (A) + TMEN (L)	$Cu^{2+} + A^- + L \rightleftharpoons CuAL^+$	13.50 ± 0.07

Table 2. Hydrolytic Decomposition of Soman, DIMEBU and DFP by Cu(II) Chelates of Glucosamine Oligomers*

Chelate System	Chelate Stability, Log β	Percentage of Total Cu(II) in the Respective Forms at pH = 7.0		Hydrolysis (n moles/min)		
		Cu(II)	Cu(II)-Chelate	Soman	DIMEBU	DFP
Cu(II)-Glucosamine (1:1)	9.88	36.16	63.84	110	1248	25
Cu(II)-Glucosamine (1:2)	17.96	21.99	78.01	113	952	25
Cu(II)-Chitobiose (1:1)	10.5	12.08	87.92	136	1248	19
Cu(II)-Chitobiose (1:2)	17.2	3.00	97.00	80	988	13.8
Cu(II)-Chitotriose (1:1)	6.84	8.94	91.06	72	930	9.9
Cu(II)-Chitotriose (1:2)	10.83	1.67	98.33	36	796	6.9
Cu(II)-Chitotetrose (1:1)	8.24	15.15	84.85	23	311	3.6
Cu(II)-Chitotetrose (1:2)	11.91	4.71	95.29	15	357	2.9
$Cu(II) \cdot \chi H_2O$	--	--	--	51	1090	15.2

*Concentration of Soman = DFP = DIMEBU = 3 mM
where DIMEBU = 3,3-dimethylbutylmethylphosphonofluoridate.
Concentration of the Species = Cu^{2+} = 3 x 10^{-4} M; Cu(II):oligomer 1:1, oligomer = 3 x 10^{-4} M; 1:2, oligomer = 6.0 x 10^{-4} M

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Results and Discussion

Potentiometric equilibrium data for the free ligands, viz., glucosamine (GA) and methoxyglucosamine (MGA) and those for their respective metal chelates having molar combining ratios of 1:1, 1:2 and 1:3 are shown in Figure 1 where the number of moles of base added per mole of total ligand or total metal (i.e., *n*) are plotted against the correspondingly measured values of -Log [H+]. An analysis of the Cu(II)-GA.HCl curve (Figure 1) with inflections at *n* = 2.5 to 3.0 indicates the interaction of Cu(II) with GA involving the $-NH_2$ and (OH) groups of the ligand molecule. Further, the partially coordinated Cu(II)-GA (1:1) undergoes hydrolysis followed by disproportionation. Cu(II)-GA.HCl (1:2) system with an inflection at *n* = 4 is indicative of interactions of the metal ion with two moles of the ligand through the displacement of the protons from their amine- and C-1 hydroxyl groups. The hydrolytic destabilization of the 1:1 chelate has been obviated through additional coordination with a second mole of glucosamine. The Cu(II)-MGA (1:1) curve (not illustrated here) with an inflection at *n* = 3 indicates the formation of a hydrolyzed Cu(II)-MGA chelate involving the NH_2 and possibly the C-3 hydroxyl groups followed by the dissociation of a proton from the Cu(II)-coordinated water molecule. The metal-ligand interactions in the case of Cu(II)-MGA (1:2) system are similar to those of the Cu(II)-GA (1:2) except in the former case the C-3 hydroxyl group is possibly involved.

Among the secondary ligands examined, tetramethylethylenediamine (TMEN), diethylethylenediamine (DEEN), tetraethylethylenediamine (TEEN), ethylenediamine (EN) and dipyridyl (DP) exhibit additional coordination with the Cu(II)-GA (1:1) and Cu(II)-MGA (1:1) systems resulting in the formation of their corresponding ternary chelates.

An analysis of the potentiometric equilibrium curves of the Cu(II) chelates of each of the three oligomers viz., chitobiose (CB), chitotriose (CT) and chitotetrose (CTet) indicates their strong coordination with a 1:1 and 1:2 molar stoichiometry (Figure 2). The Cu(II)-Biose-TMEN (1:1:1) ternary chelate system indicates the possible involvement of two amine groups and a hydroxyl from chitobiose and two amine groups from TMEN.

The thermodynamic equilibrium constants for the formation of Cu(II) chelates with the glucosamines in the combined presence of the different bidentate monoamines are shown in Table 1.

The EPR investigation of the Cu(II)-chelates were carried out on ten binary and six ternary systems. The data are summarized in a Peisach/Blumberg style plot (Figure 3) consisting of averaged values of All and gII derived from the EPR spectra. It indicates clustering in three g value regions: gII = 2.24 to 2.25, gII = 2.30 and gII = 2.40 to 2.42. The Cu(II) aquo complex is in the last cluster. On the basis of the observed shift in gII values of the binary and ternary chelates, a predominant involvement of nitrogen coordination could be inferred.

The CD spectra of Cu(II)-GA-TMEN and Cu(II)-MGA-TMEN ternary chelates in the charge transfer (400 to 250 nm) and d-d transition (800 to 400 nm) regions are illustrated in Figure 4. The results show a reversal of the peak from (+) to (-) indicating a possible change in the geometry of the chelates. The λ_{max} for both of the chelates are similar indicating that ligand-Cu(II) interaction has not appreciably been altered.

The hydrolytic decomposition of Soman, DFP and 3,3-dimethylbutylmethyl-phosphonofluoridate (DIMEBU, and agent analog) by the Cu(II) chelates of the three oligomers were investigated and the results are summarized in Table 2. It is of interest to note that the Cu(II)-Biose chelate has shown a relatively larger agent hydrolysis rate than the Cu(II)-Triose and Cu(II)-Tetrose (1:1 and 1:2) chelates.

The data generated on the hydrolytic decomposition of Sarin (GB), Soman (GD) and diisopropyl phosphorofluoridate (DFP) by a number of Cu(II)-chelates are reported in Tables 3 and 4. Values of the stabilities of the metal chelates and their corresponding agent hydrolysis rates along with the percent distribution of the different chelate species are summarized in Tables 3 and 4. For the chemical agents, GB and GD, the rates of hydrolysis by the Cu(II)-chelates follow the order: Cu-TMEN > Cu-TMEN-GA > Cu-DEEN > Cu-GA (1:1) ≈ Cu-DP > Cu-GA (1:2) > Cu-DP-GA > Cu-DAP. For the hydrolysis is of DFP, the rank order is as follows: Cu-TMEN > Cu-TMEN-GA ≈ Cu-DEEN ≈ Du-DP > Cu-GA > Cu-DP-GA > Cu-GA (1:2) > Du-DAP. GB is relatively more rapidly hydrolyzed than GD. Further, GB and GD are hydrolyzed faster, (i.e., 4 and 16 times) than DFP.

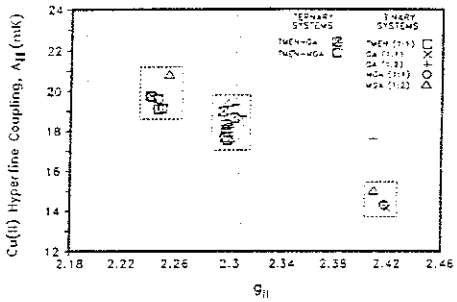

Figure 3. PLOT OF g_{II} VERSUS A_{II} FOR ALL THE BINARY AND TERNARY SYSTEMS STUDIED. THE HYPERFINE COUPLING CONSTANT IS IN mK (10^{-3} cm^{-1}).

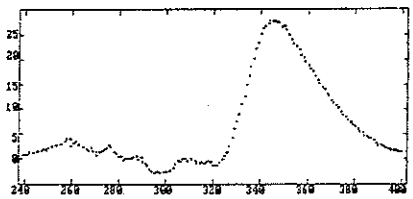

FIGURE 4A. CIRCULAR DICHROISM OF Cu-GA-TMEN (1:1:1) CHARGE TRANSFER REGION 400nm-240nm

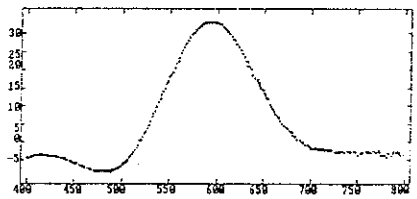

FIGURE 4B. CIRCULAR DICHROISM OF Cu-GA-TMEN (1:1:1) d-d TRANSITION REGION 800nm-400nm

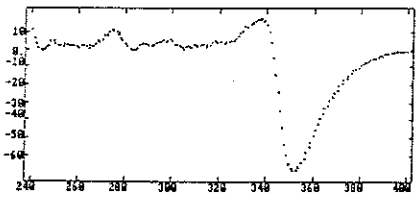

FIGURE 4C. CIRCULAR DICHROISM OF Cu-MGA-TMEN (1:1:1) CHARGE TRANSFER REGION 400nm-240nm

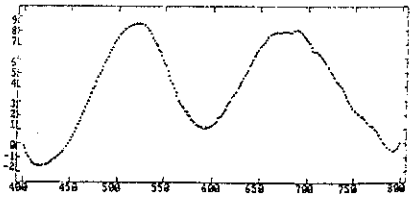

FIGURE 4D. CIRCULAR DICHROISM OF Cu-MGA-TMEN (1:1:1) d-d TRANSITION REGION 800nm-400nm

Table 4. Effect of

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Cu(II)-MGA-TMEN

*Concentration of
Buffer Medium =
Temperature = 2

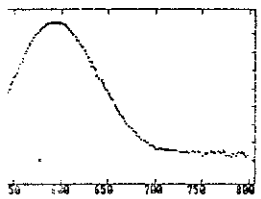
Table 3. Distribution of Cu(II) Glucosamine Chelates at pH 7.2 and their CW-Agent Hydrolyzing Characteristics

System	Chelate Stability Log β_2	Stoichiometry	% of Total Cu(II) in the Respective Chelate Forms	CW-Agent Hydrolysis μmoles/min		
				GB	GD	DFP
Cu-TMEN (1:1)	7.57	1:0 1:1 1:2	4.8 92.8 2.4	28.9	27.9	2.53
Cu-TMEN-GA (1:1:1)	16.34	1:0:0 1:1:0 1:2:0 1:0:1 1:0:2 1:1:1	0.3 23.3 2.7 8.8 4.4 60.5	26.8	16.3	1.67
Cu-DEEN (1:1)	9.05	1:0 1:1 1:2	4.5 93.4 2.1	18.6	11.9	1.57
Cu-GA (1:1)	9.88	1:0 1:1 1:2	12.4 79.4 8.1	11.3	5.31	1.04
Cu-DP (1:1)	7.11	1:0 1:1 1:2	30.3 39.4 30.3	10.3	6.39	1.64
Cu-GA (1:2)	17.96	1:0 1:1 1:2	0.6 46.9 52.5	7.99	3.26	0.44
Cu-DP-GA (1:1:1)	15.94	1:0:0 1:1:0 1:2:0 1:0:1 1:0:2 1:1:1	0.5 5.7 35.6 21.7 14.3 21.2	5.78	2.62	0.73
Cu-DAP (1:1)	9.90	1:0 1:1 1:2	9.3 87.8 2.9	1.98	0.99	0.04

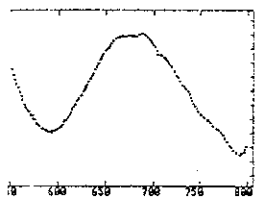
Table 4. Effect of the Nature of the Cu(II) Chelates on the Catalytic Hydrolysis of CW Agents*

Chelate System	Percentage of Total Cu(II) in the Respective Forms at pH = 7.2		Hydrolysis (μmoles/min)		
	Cu(II)	Cu(II)-Chelate	Sarin	Soman	DFP
Cu(II)-Glucosamine (1:1) (GA)	12.4	79.4	11.3	5.31	1.04
Cu(II)-Glucosamine (1:2) (GA)	0.6	52.5	8.0	3.26	0.44
Cu(II)-Methoxyglucosamine (1:1) (MGA)	18.0	82.0	8.8	5.10	1.01
Cu(II)-Methoxyglucosamine (1:2) (MGA)	3.6	27.3	8.2	5.00	0.50
Cu(II)-TMEN (1:1)	4.6	92.8	28.9	27.9	2.53
Cu(II)-GA-TMEN (1:1:1)	0.3	60.5	26.8	16.3	1.67
Cu(II)-MGA-TMEN (1:1:1)	1.0	14.9	36.6		

*Concentration of the Agent = Chelate = 4×10^{-3} M
Buffer Medium = 2×10^{-2} M; Pipes (with 0.4 M KCl), pH = 7.2
Temperature = 25°C



I DICHROISM OF Cu-GA-TMEN (1:1:1)
RT:ON REGION 800nm-400nm



DICHROISM OF Cu-MGA-TMEN (1:1:1)
TION REGION 800nm-400nm

The above discussed rank order of the agent hydrolysis rates suggest that a simple correlation based on the chelate stabilities alone is not possible. It is, therefore, more appropriate to compare the rank order of the hydrolysis rates with those of the percent distribution of the different species, i.e., aquo Cu(II) ion, Cu(II)-ligand (1:1) and (1:2) chelates and the ternary chelates of Cu(II)-glucosamines and the different bidentate amines at pH 7.2 at which the agent hydrolysis reactions were carried out.

For example, the rank order based on the percent distribution of aquo-Cu(II) ion in the different (Cu(II) chelates examined is:

Cu-DP > Cu-GA > Cu-DAP > Cu-TMEN > Cu-DEEN > Cu-GA > Cu-DP-GA > Cu-TMEN-GA (see Table 3)

Likewise, if the rank order for each of the different species of interest in the Cu(II) chelates examined in this study (Table 3) is compared with the observed rank order of the agent hydrolysis rates, it becomes evident that neither the aquo-Cu(II) ion nor the different Cu(II) chelates alone could be considered to be the predominant moiety solely responsible for the catalytic activity.

However, when the mode of coordination of the chelates and the steric factors of the ligands bound to the Cu(II) ion are considered, it appears that bidentate chelation by neutral amines with alkyl substitution on the amine nitrogens favors catalytic activity. Further, the hydrolytic destabilizing tendency of the glucosamine chelate is obviated through the coattachment with an additional mole of a secondary ligand and the concomitant formation of a ternary chelate. The fact that among the Cu(II)-glucosamine chelates, Cu(II)-TMEN-GA shows the maximal agent-hydrolysis activity highlights the importance of stabilizing the Cu(II)-GA chelate catalyst with a secondary ligand such as TMEN which is associated with appropriate steric factor that might facilitate the Cu(II)-chelate catalyst to react optimally with the substrate, viz., the agent. Two alternate mechanisms can be considered for the catalytic action of the Cu(II)-TMEN-GA ternary chelate along the lines proposed by Martell et al.: (1) an interaction of the metal chelate catalyst with the substrate agent followed by an attack of this complex by hydroxide ion; (2) a push-pull mechanism involving the hydroxo-Cu(II)-ternary chelate both of which are illustrated in Figures 5 and 6. Both of the above mechanisms invoke hexacoordination for Cu(II) in its chelates. The latter of the two, i.e., push-pull mechanism involving the hydroxo-Cu(II)-ternary chelate appears to be consistent with the data generated in this research.

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